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Relationship Between Heparin Anticoagulation and Clinical Outcomes in Coronary Stent Intervention

Observations From the ESPRIT Trial

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OBJECTIVES We evaluated the relationship between the degree of heparin anticoagulation and clinical efficacy and bleeding in patients undergoing contemporary percutaneous coronary intervention (PCI) with stent implantation.

BACKGROUND Despite universal acceptance of heparin anticoagulation as a standard of care in PCI, considerable controversy still exists regarding the appropriate dosing of heparin.

METHODS The study population (n = 2,064) comprised all patients enrolled in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial. The index activated clotting time (ACT) was defined as the ACT measured after the last heparin dose and before first device activation and was correlated with outcome and bleeding events.

RESULTS No association was observed between decreasing ACT levels and the rate of ischemic events in the treatment or placebo arms. The incidence of the primary composite end point (death, myocardial infarction, urgent target vessel revascularization, and thrombotic bailout glycoprotein IIb/IIIa inhibitor therapy at 48 h) was actually lowest in the lowest ACT tertile for both the placebo (10.0%) and treatment groups (6.1%). When analyzed by tertile, major bleeding rates did not increase in the lowest ACT tertile in patients given placebo (0.6%) versus those receiving eptifibatide (0.7%). Major bleeding rates increased as the ACT increased in the eptifibatide-treated patients.

CONCLUSIONS Ischemic end points in patients undergoing contemporary PCI with stent placement do not increase by decreasing ACT levels, at least to a level of 200 s. Bleeding events do increase with increasing ACT levels and are enhanced with eptifibatide treatment. An ACT of 200 to 250 s is reasonable in terms of efficacy and safety with the use of contemporary technology and pharmacotherapy. (J Am Coll Cardiol 2003;41:386–93) © 2003 by the American College of Cardiology Foundation

Since the first coronary angioplasty procedure performed more than two decades ago, intravenous unfractionated heparin has been the cornerstone of antithrombotic therapy during percutaneous coronary intervention (PCI). Despite universal acceptance of heparin anticoagulation as a standard of care in coronary interventions, there is still controversy about the appropriate dosing of heparin. Reports evaluating heparin anticoagulation during PCI have primarily consisted of registry reports or small case-control studies (1–4), with analyses of a larger experience focusing on balloon angioplasty trials (5). The purpose of this study was to evaluate the relationship between the degree of anticoagulation achieved with heparin and clinical efficacy and bleeding in patients undergoing PCI with stent placement.

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METHODS

Study population. To represent the current practice of PCI with stent placement, we chose patients enrolled in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial for our study population. The details of the ESPRIT trial have been previously published (6). Briefly, ESPRIT was a randomized, double-blinded, placebo-controlled, parallel-group, clinical trial conducted at 92 centers in the U.S. and Canada. Patients included in the study had coronary artery disease and were scheduled to undergo PCI with stent implantation in a native coronary artery. In the opinion of the treating physician, these patients would not be routinely treated with a platelet glycoprotein (GP) IIb/IIIa inhibitor during PCI. The enrollment period was from June 3, 1999 through February 4, 2000. Patients were randomly assigned to receive placebo or eptifibatide treatment. Among the 2,064 patients enrolled in ESPRIT, the baseline demographic and angiographic characteristics were balanced between the placebo and treatment groups. The index activated clotting time (ACT), according to patient characteristics, is shown in Table 1. Approximately 20% of

Abbreviations and Acronyms

ACT = activated clotting time
CK-MB = creatine kinase, MB isoenzyme
ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial
GP = glycoprotein
IMPACT-II = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II trial
MI = myocardial infarction
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction trial
TVR = target vessel revascularization

patients were classified as having an acute coronary syndrome within 48 h or acute ST-segment elevation myocardial infarction (MI) within seven days before the intervention. More than 98% of patients randomized underwent PCI; at least one stent was placed in 97.2% of these PCI patients. More than 20 stent types were used during the course of the study. Over 97% of patients received a thienopyridine, with clopidogrel being administered in 98% of cases.

Study protocol. The ESPRIT protocol stipulated that patients receive pretreatment with aspirin and a thienopyridine (either ticlopidine or clopidogrel, with use of a loading dose) on the day of randomization, before the initiation of PCI. A weight-adjusted heparin regimen was recommended (initial bolus of 60 U/kg, not to exceed 6,000 U) to target an ACT of 200 to 300 s. For patients who had received an intravenous heparin infusion within the previous 6 h, ACT was determined on arrival to the laboratory. If the ACT was <200 s, additional heparin was administered according to the following guidelines: ACT <150: 40-U/kg bolus; 150–174: 25-U/kg bolus; and 175–199: 10-U/kg bolus. The ACT measured after the last heparin dose and before the first device activation was defined as the "index" (maximum pre-procedural) ACT.

The study drug was started immediately before the initiation of the PCI procedure; all PCI procedures were performed according to local standards. High-pressure balloon inflation for stent deployment was encouraged, and any stent type with regulatory agency approval could be implanted. Patients were allocated to receive placebo or eptifibatide in a 1:1 distribution. The eptifibatide dosing consisted of a bolus dose of 180 μg/kg, immediately followed by a continuous infusion of 2.0 μg/kg per min (or 1.0 μg/kg per min in patients with serum creatinine >2 mg/dl). A second bolus dose of eptifibatide of 180 μg/kg was administered 10 min after the first. The infusion continued until hospital discharge or up to 18 to 24 h. Activation of the PCI device (balloon, stent, or other interventional device) was permitted at any time after the first bolus.

Baseline blood counts (hemoglobin, hematocrit, and platelet count) and cardiac enzymes were obtained before device activation. Blood counts were measured at 24 h and when there was any clinical suspicion of bleeding; cardiac enzymes were measured at 6, 12, 18, and 24 h and analyzed in the core laboratory. The index ACT was used to reflect the anticoagulation state at the time of device activation. Vascular access sheaths were to be immediately removed with either a femoral arteriotomy closure device or external

Table 1. Index Activated Clotting Time by Characteristics of Patients

	ACT	p Value*
Gender		
Females	270 (235, 309)	0.138
Males	266 (231, 306)	
Country		
U.S.	265 (231, 304)	0.021
Canada	273 (234, 320)	
History of MI		
Yes	270 (234, 307)	0.252
No	265 (231, 306)	
Previous PCI		
Yes	273 (239, 307)	0.026
No	265 (230, 306)	
Previous CABG		
Yes	269 (234, 308)	0.821
No	267 (231, 306)	
Diabetes		
Yes	267 (232, 309)	0.977
No	267 (232, 306)	
Hypertension		
Yes	266 (232, 306)	0.568
No	269 (232, 307)	
Hypercholesterolemia		
Yes	267 (234, 307)	0.201
No	266 (230, 306)	
Current smoker		
Yes	263 (227, 302)	0.080
No	269 (234, 309)	
Stable angina		
Yes	271 (235, 312)	0.043
No	265 (230, 304)	
Unstable angina/NQMI		
2 to 180 days		
Yes	267 (232, 311)	0.946
No	267 (231, 306)	
Within 2 days		
Yes	257 (224, 291)	0.001
No	269 (233, 310)	
ST-segment elevation MI within 2 days		
Yes	246 (212, 286)	< 0.001
No	268 (233, 308)	
Positive functional test only		
Yes	279 (244, 313)	0.004
No	265 (231, 306)	
Other anginal equivalent		
Yes	278 (230, 309)	0.899
No	267 (232, 306)	

*Wilcoxon test of differences in ACT for categorical variables. Two continuous measures were also examined. Age was not statistically significantly correlated with ACT ($r_s = 0.03$, $p = 0.125$). Weight was significantly correlated ($r_s = -0.08$, $p < 0.001$). Data are presented as the median value (25th and 75th percentiles).

ACT = activated clotting time; CABG = coronary artery bypass graft surgery; MI = myocardial infarction; NQMI = non–Q-wave myocardial infarction; PCI = percutaneous coronary intervention.

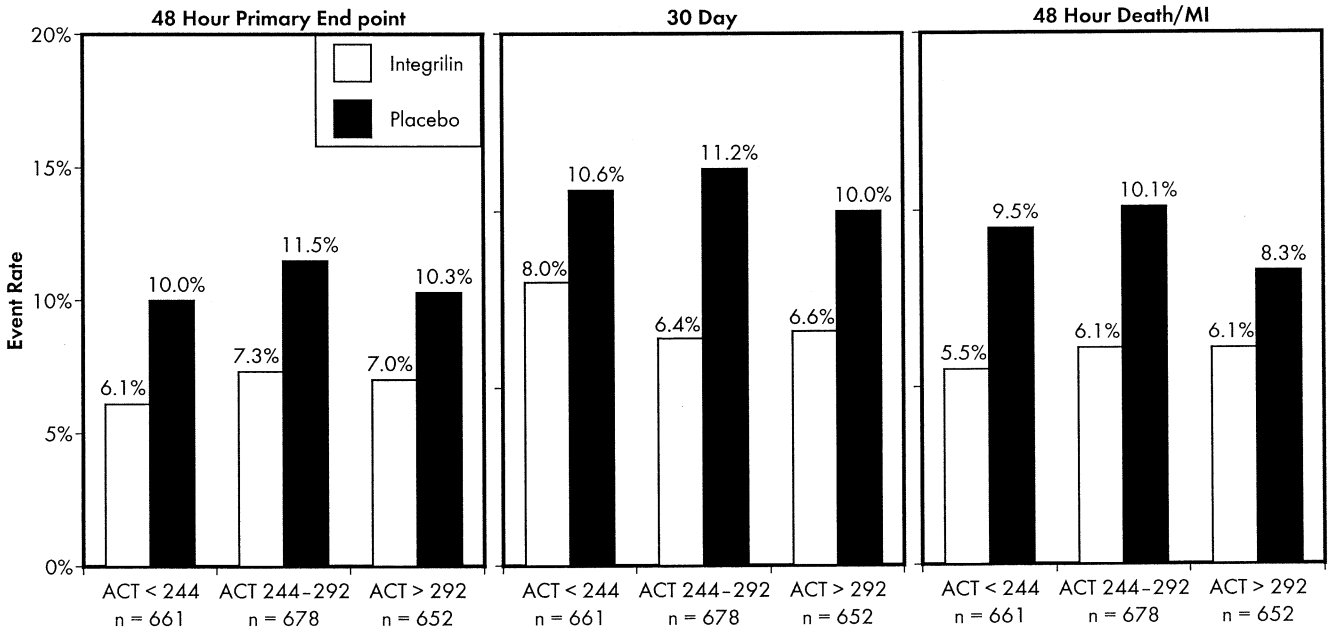

Figure 1. Clinical efficacy of the composite end point of death, myocardial infarction (MI), urgent target vessel revascularization (TVR), and bailout to open-label treatment for thrombosis; secondary end point of 30-day death, MI, and urgent TVR; and 48-h death or MI by tertile of index activated clotting time (ACT).

compression for hemostasis within 3 to 4 h after completion of the PCI procedure.

End points. For this study, ACT values were correlated with the following: the incidence of the primary ischemic end point for ESPRIT (death, MI, urgent target vessel revascularization [TVR], and thrombotic bailout GP IIb/IIIa inhibitor therapy at 48 h); the secondary composite end point of death, MI, and urgent TVR at 30 days; and the occurrence of death or MI at 48 h. In the ESPRIT trial, enzymatic MI was defined as the recording of at least two creatine kinase, MB isoenzyme (CK-MB) concentrations greater than or equal to three times the upper limit of normal within 24 h after PCI. Clinical MI was an event reported by a site investigator and adjudicated by the Clinical Events Committee. Bleeding events were quantitatively classified as major or minor according to the Thrombolysis in Myocardial Infarction (TIMI) trial criteria (7). To account for the influence of red-cell transfusions on measured hemoglobin values, the estimated decreases in hemoglobin were adjusted according to the technique of Landefeld et al. (8).

Statistical methods. The continuous ACT variable is presented as the median value and 25th and 75th percentiles. Wilcoxon tests of differences in ACT were performed for categorical variables. The associations between ACT and outcomes were illustrated by dividing ACT into tertiles and presenting the event rates within each level of ACT. The relationship between ACT and outcome was determined by using restricted cubic spline transformations, which allowed the relationship to be flexible across levels of ACT (9). If the association was linear, ACT alone was used in all future tests. If the association was nonlinear, an appropriate transformation was found. Because the associations between ACT and outcomes were linear in the ESPRIT data, a transformation was not required. The associations of ACT and outcomes were tested by using logistic regression modeling techniques and univariate statistics after adjusting for baseline factors. Multivariate models of the primary outcome and 30-day death or MI were previously developed by using baseline clinical and angiographic factors.

Interaction terms were used to test the differential effect of eptifibatide on the relationship between ACT and outcomes. If the interaction term was significant, tests within each treatment arm were used to evaluate the ACT association. If the tests were nonsignificant, evidence was insufficient to assume that the relationship between ACT and outcomes was any different between the two treatment arms.

Rates of bleeding and ACT levels for ESPRIT patients were compared with those of patients enrolled in the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT)-II trial (10) by using the Pearson chi-square test and Wilcoxon rank-sum test. All tests used $p < 0.05$ for the critical value of statistical significance. Analyses were performed by using SAS statistical software (SAS Institute, Cary, North Carolina).

RESULTS

The incidences of the primary composite end point; secondary end point of death, MI, and urgent TVR at 30 days; and death or MI at 48 h are shown by the index ACT levels in Figure 1. The degree of heparin anticoagulation, as measured by ACT, did not significantly affect the rate of

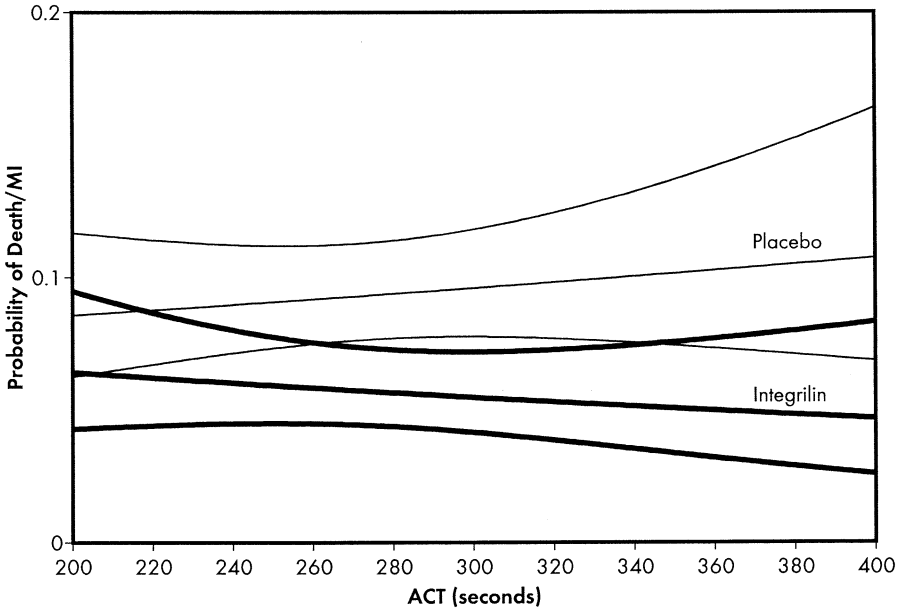

Figure 2. Probability of 48-h death or myocardial infarction by index activated clotting time (ACT) for patients receiving treatment versus placebo in the ESPRIT trial.

ischemic events. This lack of association was also similar for the treatment and placebo arms ($p = 0.430$), and the results were similar after adjusting for baseline factors. In the placebo group, the incidence of death or MI at 48 h was similar among patients distributed by tertiles of maximum ACT: 9.5% in the lowest tertile, 10.1% in the middle tertile, and 8.3% in the highest tertile. This same trend was seen when the incidence of death or MI at 48 h was analyzed by continuous ACT values (Fig. 2). The incidence of the primary end point was lowest for the placebo (10.0%) and treatment groups (6.1%) in the lowest ACT tertile (Fig. 1). The relative benefit of eptifibatide treatment was also similar across the tertiles of ACT. The lowest overall event rate for the primary end point, as well as the lowest incidence of death or MI in eptifibatide-treated patients was in the lowest tertile of ACT.

An increase in bleeding was associated with increasing ACT with eptifibatide treatment, as measured by the quantitative TIMI bleeding criteria. When bleeding was analyzed by individual ACT tertiles, rates of major bleeding were similar only in the lowest tertile with placebo (0.6%) versus eptifibatide (0.7%) (Fig. 3). Differences between groups in rates of major bleeding increased as ACT increased (Fig. 4).

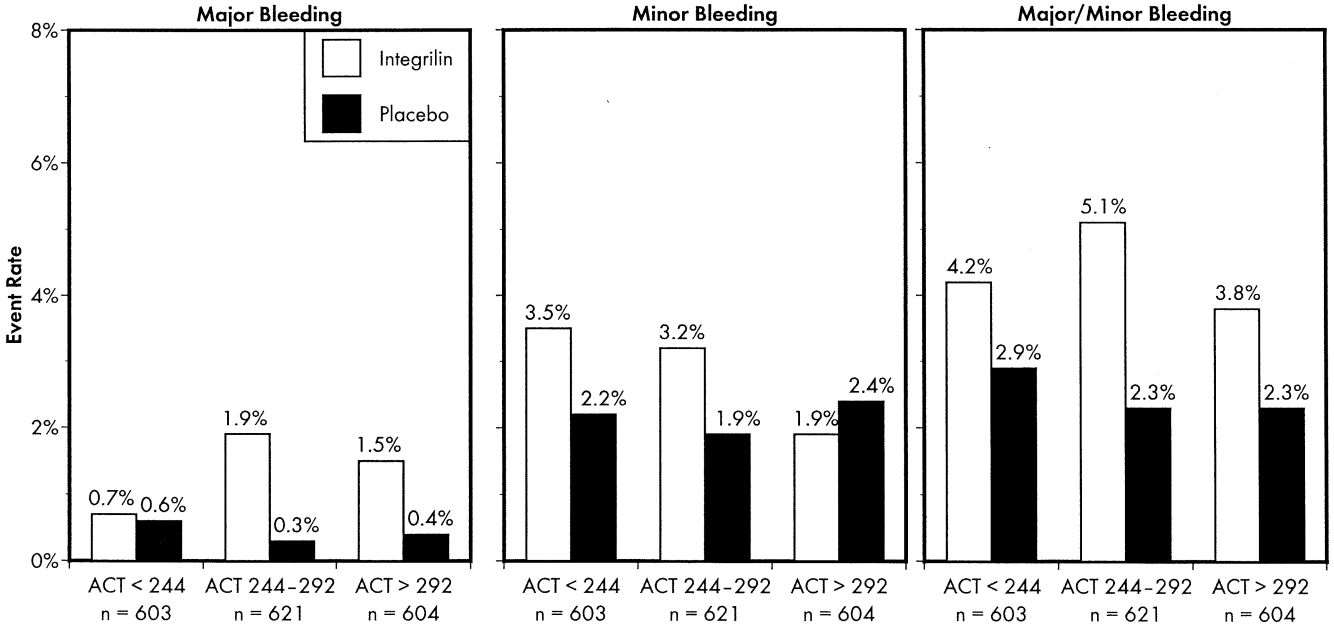

Figure 3. Major, minor, and the combination of major and minor bleeding (by TIMI criteria) by tertile of index activated clotting time (ACT).

JACC Vol. 41, No. 3, 2003
February 5, 2003:386–93

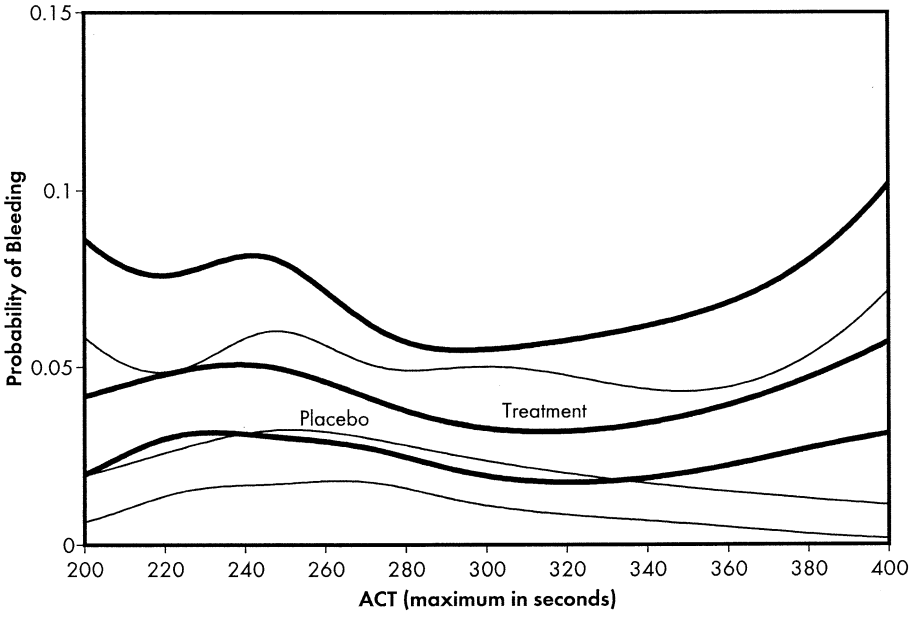

Figure 4. Probability of bleeding by index activated clotting time (ACT) for patients receiving treatment versus placebo in ESPRIT.

The relationship between ACT and bleeding, as well as between ACT and ischemic events, was further evaluated by using logistic regression modeling. Increases in ACT among ESPRIT patients were not associated with significant changes in overall bleeding rates (TIMI, major and minor) ($p = 0.940$). Eptifibatide was associated with an increased risk of bleeding, relative to placebo, after adjusting for ACT levels ($p = 0.029$)—a relationship that remained constant across all levels of ACT ($p = 0.387$). Bleeding events were increased in women (5.5% vs. 2.7%, $p = 0.004$) and in patients with peripheral vascular disease (7.4% vs. 3.2%, $p = 0.01$). No increases in bleeding rates were observed with increasing creatinine ($p = 0.817$) or in patients with a previous MI ($p = 0.309$). Bleeding rates were also calculated in terms of the amount of heparin given. The total heparin dose was not correlated to subsequent risk of bleeding ($p = 0.757$). Even after adjusting for age, weight, and gender, we found that the total heparin dose was not predictive of bleeding events ($p = 0.228$). Decreasing ACT levels, in turn, were not associated with an increased risk of death or MI in ESPRIT patients ($p = 0.965$).

Eptifibatide treatment was associated with a significant decrease in the occurrence of death or MI after adjusting for the ACT level ($p = 0.002$). The relationship between ACT and death or MI appeared to remain flat for both placebo and eptifibatide. Regression analyses were also performed to test for the association between post-procedural enzyme elevation (post-procedural CK-MB values minus pre-procedural CK-MB values) and ACT in patients receiving eptifibatide, as well as in those receiving placebo. There was no significant relationship between ACT and post-procedural enzyme elevation ($p = 0.767$) after adjusting for treatment.

DISCUSSION

The ESPRIT trial, which included the use of 6F guiding systems, coronary stents, a dual-antiplatelet regimen, and low-dose, weight-adjusted heparin, afforded us an opportunity to evaluate the relationship between anticoagulation levels and bleeding and ischemic events in a contemporary treatment setting. The incidence of ischemic events did not increase as ACT decreased, at least to a level of 200 s. Overall, major bleeding events were rare, with a total of 17. When analyzed continuously by use of a regression model, the increase in major or minor bleeding corresponding with increasing ACT did not reach statistical significance. In addition, the difference in bleeding rates between the eptifibatide and placebo arms was not statistically different in the lowest range of ACT values.

The monitoring of anticoagulation by ACT was initially described in the surgical literature for the purpose of guiding heparin dosing during cardiopulmonary bypass (11). This technique gained widespread use in interventional laboratories in the late 1980s. Based on empiric observations and small case-control studies, the initial recommendation for target ACT levels was in the range of 300 to 350 s (2,3).

In the early 1990s, a series of clinical trials of platelet GP IIb/IIIa inhibitors was conducted to evaluate the outcomes of patients undergoing PCI (10,12–15). In the Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial (12), treatment with abciximab reduced ischemic complications among high-risk patients undergoing PCI, but was associated with a doubling of the risk of major bleeding and the need for blood transfusion. In the PRecursor tO EPILOG (PROLOG) study (15), a strong trend toward a diminished risk of bleeding was shown with reductions in weight-adjusted

Table 2. Comparison of Different Heparin Doses in Clinical Trials in the 1990s

Study	Study Drug	Dates	Heparin Dose	Target ACT (s)
EPIC (12)	Abciximab	1991–1992	10,000–12,000 U/kg (maximum 20,000)	300–350
IMPACT-II (10)	Eptifibatide	November 1993 to November 1994	100 U/kg	300–350
RESTORE (14)	Tirofiban	January to December 1995	150 U/kg (maximum 10,000)	300–400
EPILOG (13)	Abciximab	February to December 1995	100 U/kg (placebo)	300
			70 U/kg (abciximab)	200
EPISTENT*	Abciximab	1996–1997	100 U/kg (placebo)	300
			70 U/kg (abciximab)	200
ESPRIT (6)	Eptifibatide	1999–2000	60 U/kg	200–300

*Source: The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998;352:87–92.

ACT = activated clotting time; EPIC = Evaluation of IIb/IIIa platelet receptor antagonist in Preventing Ischemic Complications; EPILOG = Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT = Evaluation of IIb/IIIa Platelet Inhibition for Stenting; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; IMPACT-II = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis.

heparin dosing and early sheath removal. The PROLOG study also demonstrated that, despite inhibition of platelet aggregation with GP IIb/IIIa inhibitors, local hemostasis could be readily achieved after sheath removal if heparin was first discontinued and coagulation parameters were normalized.

These findings helped shape the design of interventional studies, including ESPRIT, throughout the 1990s. The dose of heparin anticoagulation recommended in PCI trials was empirically decreased during the ensuing decade (Table 2). In ESPRIT, the placebo and treatment arms included the lowest weight-based regimen that had been used to date. The goal of ≥200 s was also the lowest target ACT that had been recommended in a clinical trial of PCI patients. By collecting index ACTs at the time of device activation, with systematic recording of hematologic parameters and cardiac enzymes in all patients after the procedure, we had an opportunity to analyze the effect of the predictor (ACT) on the outcomes (MI and bleeding) in a large number of patients.

The low overall rate of bleeding observed with the double-bolus dosing of eptifibatide was of particular interest in the ESPRIT study. The eptifibatide dose was approximately three times greater than that administered in IMPACT-II (10), a randomized study of eptifibatide in 4,010 patients undergoing an elective, urgent, or emergency coronary intervention between November 1993 and November 1994. Heparin was administered as a 100-U/kg bolus with a target ACT of 300 to 350 s in IMPACT-II. Despite the markedly increased level of inhibition of platelet aggregation in ESPRIT, however, the rates of bleeding were approximately four times lower than those observed in IMPACT-II. This difference was seen across all ranges of ACT (Table 3, Figs. 5 and 6), and the same difference in bleeding rates between the two studies was seen in the placebo arm. The significant decrease in bleeding rates reflects advances in percutaneous catheter-based technology and arterial access management over the past decade. During the ESPRIT study, 6F sheaths and guiding catheters were standard at most study sites. The ESPRIT protocol contained detailed instructions regarding arterial access sheath placement, care, and removal, as well as post-procedural care. A reduction in heparin dosing, smaller arterial access sheaths, and improved management of the access site markedly contributed to reduced rates of bleeding, despite more potent levels of platelet inhibition.

Ischemic complications in our study did not increase at the lowest levels of ACT, even in the placebo group. As shown in Figure 1, for the 48-h ischemic end points, the rates were similar across tertiles of ACT. This is the first published report of low ischemic complication rates with decreasing ACT levels in a heparin-only group of patients undergoing PCI with stenting—a finding that remained constant at both the 48-h and 30-day end points. Bleeding

Table 3. Comparison of Bleeding Risk in ESPRIT and IMPACT-II Patients Using TIMI Major/Minor Bleeding Criteria

	ESPRIT		IMPACT-II	
	Treatment Arm	Placebo Arm	Treatment Arm	Placebo Arm
Median ACT (Q1, Q3)	273 (234, 315)	263 (230, 300)	356 (324, 394)	344 (316, 380)
Major/minor bleeding	4.4%	2.4%	17.4%	14.4%
ACT (s)				
200–249	4.20%	3.75%	31.25%	18.18%
250–299	5.02%	1.63%	16.13%	13.68%
300–349	2.86%	2.88%	15.11%	13.62%
350–399	1.28%	1.89%	18.08%	15.41%
400–449	6.45%	0	18.75%	16.67%

Data are presented as the median value (25th and 75th percentiles) and percentage of subjects.

TIMI = Thrombolysis in Myocardial Infarction; other abbreviations as in Table 2.

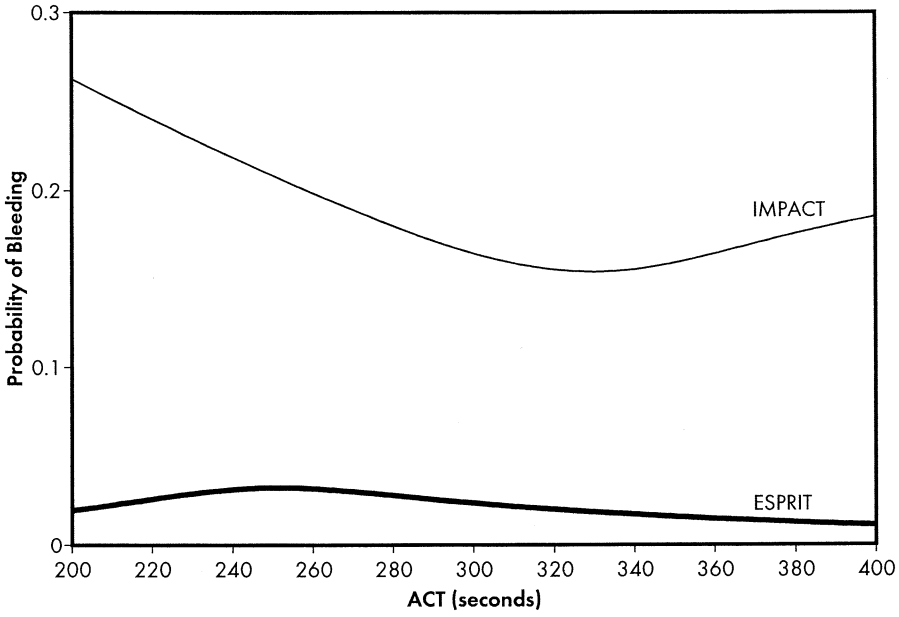

Figure 5. Comparison of bleeding probabilities between IMPACT-II and ESPRIT patients receiving placebo. ACT = activated clotting time.

was likewise low for the placebo group at lower ACT levels. This was true for TIMI definitions of bleeding as major, minor, or a combination of the two (Fig. 3).

Chew et al. (5) recently reported the results of a meta-analysis of six randomized trials of patients undergoing PCI. In this study, when the degree of heparin anticoagulation was compared with ischemic and bleeding end points, the risk of ischemic end points was progressively reduced with increasing ACT levels, with no observed upper limit of efficacy. The ACT also correlated with bleeding events, with the lowest event rates seen in the range of 325 to 350 s.

Important differences between this meta-analysis and the current study deserve emphasis. The patients analyzed by Chew et al. (5) represented a heterogeneous population with a broad range of indications for intervention, as well as available technologies at the time of the individual studies. The analysis included studies spanning almost a decade, a time during which major pharmacologic and technologic advances were made in interventional cardiology. Of the more than 15,000 patients studied, only 1,221 (7.7%) received a coronary stent. Generally, 8F or 10F sheaths were used, and only a small minority of patients received ticlopidine or clopidogrel. Compared with traditional anticoagulation regimens (16–18), these agents have been associated with significant reductions in bleeding events after coronary stent implantation. The association between ACT and

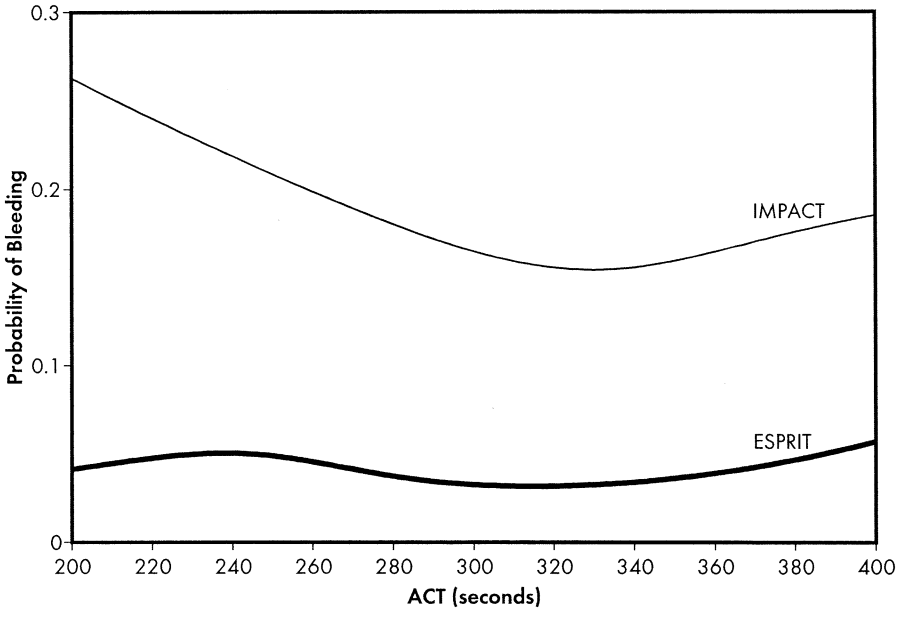

Figure 6. Comparison of bleeding probabilities between IMPACT-II and ESPRIT patients receiving treatment. ACT = activated clotting time.

ischemic complications may be more relevant in balloon angioplasty cases in which inflation times, as well as overall procedure duration, are typically longer than with coronary stenting. A similar relationship between heparin anticoagulation and the risk of abrupt closure in angioplasty patients (not undergoing routine stenting) was observed by Bittl et al. (19).

Study limitations. Patients were not randomized in terms of heparin dosing or ACT. Although an ACT of 200 to 250 s was associated with optimum safety and efficacy in this study, we cannot state definitively that this is the best possible level of anticoagulation. Whether an ACT of <200 s would have provided adequate anticoagulation could not be addressed. Bleeding rates were extremely low in this study, and we did not have adequate statistical power to detect differences in bleeding for increases in ACT. Given these low overall rates, however, it does not appear that extreme values of ACT were associated with increased bleeding. The sample size also did not provide adequate statistical power to detect differences in rare thrombotic complications, such as peripheral embolism or stroke and vascular thrombosis. However, none of these adverse events occurred in either group in the 2,064 patients in the study.

Clinical implications. This study extends our understanding of the relationship between heparin anticoagulation and important clinical outcomes in patients undergoing PCI. There was no minimum ACT below which there was a tradeoff between bleeding and ischemic events. Ischemic events did not significantly increase in the lowest ranges of ACT—a finding that remained constant for both the eptifibatide and placebo-treated patients. Based on this analysis, an ACT of 200 to 250 s appears to be reasonable in terms of safety and efficacy in a contemporary treatment setting. Further reductions in heparin dosing during PCI should be investigated in a prospective, controlled study.

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